Research Seminar?- NMR resonance studies:
Partly financed from other sources (EEC?)

—

11/11/92.

① WHO Women & Tobacco -

of note:- Claim that relative risk has increased for many smoking associated diseases, with more women smoking

Claim that women are less likely to get recommendations from physicians to give up smoking.

Claim not enough emphasis put on negative effects

—

Variance & Dissent: Presentation -

Dubious evidence of Heart and Cancer Deaths Due to Passive Smoking:
Nathan Mantel: J Clin Epidemiol 45(8):809-813. 1992.

Mantel largely criticising Glantz & Parmleys quantification of ETS causing 53,000 Heart & Cancer deaths annually in the US.
Basis of the quantification flawed on following grounds:-

① Added calculation to increase RR due to exposure outside the home'. (workplace study - sparse data - invalid reference!)

② Exaggerated RR's, taken from Repace & Lowry calculations etc etc

Dissent:

Passive Smoking Causes Heart Disease and Lung Cancer
S.A. Glantz & W.W. Parmley: J. Clin Epidemiol. 45(8):875-894. 1992

Response to Mantels paper above - largely says that Mantels claims are unsupported by quantified evidence i.e. Mantel claims that RRs are based upwards but provides no specific details to support these claims. Glantz & Parmley dismiss Mantels stance saying that it is not 'objective' but biased for the tobacco industry.
They maintain that the evidence, epidemiological, physiological & biochemical show that passive smoking causes not only lung cancer, but also heart disease.

Source: https://www.industrydocuments.ucsf.edu/docs/qscl0000

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A.E. Taylor, D.C. Johnson & H. Kazemi. 1992. Circulation 86(2) 699-701
Position statement: Environmental Tobacco smoke and Cardiovascular Disease: A position paper from the council on Cardiopulmonary and Critical Care, American Heart Association:

"Although the number of cardiovascular deaths associated with environmental tobacco smoke cannot be predicted with absolute certainty, the available evidence indicates that environmental tobacco smoke increases the risk of heart disease."

"Even though considerable uncertainty is a part of any analyses on the health effects of environmental tobacco smoke because of the difficulty of conducting long-term studies and selecting sample populations, an estimated 35,000 - 40,000 cardiovascular disease-related deaths and 3,000 - 5,000 lung cancer deaths due to environmental tobacco smoke exposure have been predicted to occur each year."

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Source: https://www.industrydocuments.ucsf.edu/docs/qscl0000

12/11/92.

~~Tokar~~ Sanner - Lyon - interest in publications - Norwegian Radium Hospital.
Norwegian Research Council - initial pilot study w 300 samples -
only in initial stages. Parameters - analysis - only ETS measureable
Retrospective - time frame not yet established.
Infant hair - high & low absorbers.
→ Research on in vitro testing - cell transformation
Oslo meeting - Nordic discussion of Environmental Tobacco Smoke.
Chuck Lister discussion - debate w industry not happily taken!

—||—

The Data:- Exposure of the order of 100 µg/m³ = very high exp.

Publications re air concentrations of nicotine - range!
Calculation of upper limit?
Mass of tobacco / cig.
%age left in filter (range)
%age left in ash (range)

(Pass onto ON some publications on ranges measured.)
200 & 2000 linear over ~~12~~ hours
High & low adsorbers - how strongly bimodal?

Passive smoke unit - must be linear w time & concentration.
Theory - equilibrium v saturation?

—||—

Linearity w dose.
Cotinine - dosed method for analysis of cotinine in hair - primary sample
= no cotinine but no investigation further. (HGCMS)
To establish whether internal or external.
Intent to analyse for cotinine in 80 subjects. (same samples)
Measurement of Melanin - as well? - to explain low & high.
Effect of washing on ST accumulated nicotine.
Priorities: ① cotinine in 80 subjects.

—||—

Publ. 1. - Chamber trials ST, high dose -
should point out high dose, short term no saturation - should
raise questions about lower dose, longer exposure. - i.e. more relevant.

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Source: https://www.industrydocuments.ucsf.edu/docs/qscl0000

Pub 2. – Chamber trials – low dose model linearity. (1&2 combined] -1

Pub 3 80 subjects - 20, 200, 2000 + office exposure! -2
+ washing information, (for later = cotinine/melanin).

What Journal should these be published in? [Finnish Health Journals]

Clinical Chemistry:- [Pharmacology & Toxicology]

¿Biomonitoring Journal – ?

Pub 4. GCMS methodology for Nicotine & Cotinine. -3

Timeframe? – Jan/Feb = Drafts ready for review.

[another meeting to discuss in February] ∴ March for submission

Next year – $100,000

① ~~tal~~ Exposures over time – washing: (saturation levels)

[② External / internal levels:-]

Extrapolating back – what factors affect accumulation in hair?

Exposure time – 1 year study. – 5 μg/m³. – establish plateau level.

Sample – duplicate each month. Nº of subjects = 24 hours from each subject –

∴ at least 4.

Could we pre-study for low & high absorption?

Prob not possible to use same region of hair for all 24 samples:

Hair Conference Dec 10-12 1992 Genoa – "Hair Analysis as diagnostic tool for drugs of abuse investigation." (see copy):-

109000 – included consultancy – tax disadv – in Norway:- (as previously)
(More efficient use of the money!!)

May 1993 – Norwegian Research Council.

*Copy of data to PEM to Nilsen *

Discussion of low absorber high absorber differences – All discd

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Source: https://www.industrydocuments.ucsf.edu/docs/qscl0000

Apr 10th – 5 cigs : Ratio = 16 ≡ 7000 ng. ≡ ~~7 ng~~ 750 ng.
8h at 1 l/min – 24 x 60 ~~x 24~~ =

480 l. ~~750~~ / 480

Nicotine disappearance from a room – see Newcastle data?!
Could monitor with fresh XAD4 column after exposure has terminated.
Know that 16hrs later exposure has decreased to virtually zero
How long should pump run continuously.

Articles No 64544; 64545; 64546
"Ethnic Differences in Nicotine Exposure"
A series of letters commenting on previous publications in this area –
[American J. Publ Health; 1992; 82(8): 1171–1173]

① From W.J. McCarthy et al.
Offers possible explanations for ethnic differences between blacks hispanics & whites as reported by ~~Perez-Stable~~ Wagenknecht et al (A.J.P.H 1990; 80: 1057–
Suggests ① smoking topography may differ
② ETS exposure may differ
③ Mentholated cigarette use (higher in blacks)
④ SCN measurement of smoking status could be affected by dietary differences

② Pérez-Stable et al respond accepting the possibility that smoking topography & ETS exposure may have influenced their results but felt that they were likely not to influence the overall finding. They did however accept that the observations should not be prematurely explained in terms of genetically based metabolic diffs but should be examined further.

③ Wagenknecht responds to ①: Considers that mentholated ciggs were measured and may explain some, but not all, of the diffs. SCN more likely to exaggerate the effect due to blacks in general having higher dietary contribution. Topography also suggest black smoke less of cigarette than whites. ETS will have little influence.
∴ Conclude need further investigation.

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Alistair Woodward & A.J. McMichael: Eur. J. Cancer [redacted] 1991; 27(1): 11-29

Passive smoking and cancer risk: The Nature and use of epidem. Evidence.

The authors review the interpretation of the evidence re ETS & Cancer rather than the evidence itself. As most of the evidence is on lung cancer, rather than any other cancers, and is almost entirely on Epidemiologic evidence, they concentrate on the use of epidemiology and its strength in identifying cause.

Under the scientific premise that there is no proof of cause they conclude that the epidemiology to date is sufficiently consistent to indicate a causal relationship To this extent they review & disregard the following criticisms w.r.t. this argument:-

① "Statistical significance" - significance of individual studies not important compared to consistency.

② Extrapolation of dose response - ETS epidemiologically RR are too high for the extrapolation of dose from Active smoking. but 'linear' Model may not be appropriate & do not know proportion of "carcinogenic agents" in MS to ETS.

③ Misclassification - considerable review of data from Wald, Wells Lee etc - leads them to conclude that it is not sufficient to explain the effects. In fact the effect of misclassification is likely only to be sig in population with high background female smoking - i.e would not apply to Japan / Greece etc.

④ Publication bias - reviewed all available evidence & found no publication bias in ETS studies - furthermore evidence may suggest publication towards -ve studies.

⑤ Scientific proof - discusses what is 'sufficient evidence' uses Australian Council case & AFCO cases as legal tests of proof of Cancer risk.

Concludes that weight of epidemiologic evidence indicates a positive lung cancer risk.

Also emphasises that data could & should be considerably improved by better establishing exposure.

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Source: https://www.industrydocuments.ucsf.edu/docs/qscl0000

16/11/92.

Write up Nat. Epidemiology Meeting. - circulate Richm. IN V. - Evan Gregg
" Nilsen Meeting
" Warren discussions. Send card to Warrens.
Send info to Claire Purcell
Write up INBIFO Meeting
Ring M.C. Nam
Ring Wendy Burns
Ring / Profs to Spain

17/11/92. INBIFO.

1. Next annual study in January:

Concern why increase so dramatic at 3rd sampling.

New study: Brown Norway + Albino (SD - unpigmented)

? Will melanin influence uptake?

Slightly older rats to improve hair growth = 64 (prev. = 57 days')

Osmotic pump - several doses 0,5,10,20 mg/(kg×d) (+3 weeks ≈ 85 days) (instead of 4 dose prev.)

(N.B normal dose due to weight increase) Brown Norway ≈ 200g
SD ≈ 300g

Total of 36 animals rather than the original 6.

36 rats - grouped as follows:-

for each dose 3 rats in metabolic cages individual } 5 rats/dose.
1 rat in wire mesh cage to control

Except for 0 dose = no need for wire mesh pair!

Metabolic cages - urine daily

? what is daily nicotine uptake - is answer 3rd time point diff from 1st expt. ?

Parameters - measured 7, 7 & 7 days

nicotine & cotinine measured in hair.

(Snyder et al v. high nicotine concentration but very little ≈ 2% of nic content - which is the same as found in smoke)

Could be used as an internal control for urine contamination.

Urine collected every 24hrs for met cages [- for others only 1x. to check pump]

Determine Nic & Cotinine. [other metabolites? for other studies]

Plasma conc determined on last day - nic & cotinine.

Measure remaining solution in pump & conc of remaining solution [In 1st expt found ↓ in conc which may indicate some description of nicotine in pump -]

Problem with birthdate - require exact same age litter dates for all 36 rats which may be problematical as suppliers usually supply with wt!

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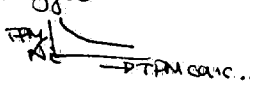
Source: https://www.industrydocuments.ucsf.edu/docs/qscl0000

Experiment to establish what binds to hair? Hair + cocktail.
Results should be out at end of February.
If possible expose some xtra brown rats to ETS -
Monday - expose shaved rat hair to SS smoke in conditioning room.
(Nic conc ≈ 1µg/m³) 3 weeks - samples after 1, 2 & 3 weeks.
daily exposure ≈ 8½ hours. - in bags - to avoid TPM. -
but should also look for raw hair with TPM deposition.
Washing experience - rats from systemic exposure = no wash off
smokers hair ≈ 20% washed off - but an early expt w rat hair
exposed to ETS for 1,2,3 weeks it all washed off

Cotinine % of Nic in MS = 0.6% SS = 0.7 - 0.8% (TPM)
(Published data of same order) - all in condensate.
Neurath publication criticised by RJR - artefacts due to adsorption on
the equipment. Relative OK but quantitative is off!
100% in vapour phase - none in particulate - evaporates from particles v. v. fast.

Markers for solanesol - for particulate 3-ethyl-pyridine for gaseous phase.
Passive smoking unit? -
Particle phase - solanesol. (not for biomonitoring). Solanesol as biomon.
Gas phase - CO, 3-ethenyl pyridine - adducts HbCO → biomonitoring.
Nicotine - nicotine = behaves strange = totally independent of gas. -

Ratio of nicotine to other components may differ considerably depending on circumstances of exposure! (freshness & concentration of ETS) - the larger (chronic) exposures should reduce this effect.
Nicotine % of TPM will vary w TPM conc alone



Systemic uptake of nicotine into human hair.
Testing with human subjects - implications
Nicotine pharmacological only biomedical research - (prescription drug)
∴ = Biomedical research w regulations applying:
Risk - benefit balance

Proposal: - Human study: -
Objective - Is there systemic uptake?
- Is there a relevant contribution of a systemic uptake to the nicotine concentration found in smokes hair?

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Source: https://www.industrydocuments.ucsf.edu/docs/qscl0000

What is "relevant" - quantitate say roughly 10% of contribution of hair.
Is there a significant contribution to nicotine in hair for non-smokers?
Has to be answered by extrapolation from smokers. - or could use non-smokers with chewing gum?
Extrapolation from rat studies suggests human hair should have only 1% contribution from systemic.
Current study design.
3 volunteers: ; males; healthy smokers approx 1 per day (≈1mg/cig)
Application w nicotine patch - 21mg over 24h (≈ 0.3mg/kg/d).
duration of application = 8 days.
Condition - no smoking; nicotine free atmosphere for 14 days.
i.e. clinical situation (smoke free hotels; sailing boats).
Beard hair. - every 48h = enough material for analysis.
Samples to be taken 3 ~~days~~ times before expt starts
3 times hair grown without any nicotine exposure (smoke free)
After apply nicotine patch = 3 samples
Determine Nicotine & cotinine in hair (10x total!)
Plasma conc. Nic & cot. day 15 or later; 8h after applying patch
(because conc reaches maximum at this time)
Saliva concentration - less invasive than blood plasma. - claims quite good correlation.

Problem of sweating? - transfer on hands!
Nicotine concentration in rooms.
[CO in expired air].

Cerutti data on fos/mug etc
Concentration effect w PBS - genotoxicity at 0.3 puffs/ml.
Smoke kinetics similar to okadaic acid (phosphatase inhib)
Parallel bed smoke & okadaic acid
Nuclear Run off (P32). - No induction of c.fos promotors by O.A or PBS

mRNA cfos 1/2 life increased by PBS & O.A.
Inhibition of protein synthesis by PBS which prevents cfos degradn?
= Yes but only slightly ⇒ 63%
Dose response protein band. - Hemoxygenase

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Source: https://www.industrydocuments.ucsf.edu/docs/qscl0000

Look for inhibition of phosphatases 1 & 2A. = yes very similar.
but slow needs long exposure.
Active oxygen compared to PBS - No! ½ life of c-fos AO like
but key is that cfos activation is inhib. by catalase w Oxygen Rad
but not w PBS. X/XO/ like TPA & growth factors in behaviour.
Catalase no effect on PBS induced cfos mRNA.

Fenton derived radical inhibitor - o-Phenanthroline. = ~~effects~~
No effect on cfos mRNA expression due to PBS but entirely inhibits
PBS induced SS breaks.
Glutathione - GSH ↓ in PBS. 100 - 366%
cysteine residues - hemoxygenase Haem oxygenase - Fe^{2+} radicals
Sulphydril molecules - haem oxygenase
oxygen radicals =
13 cystein residues in phosphatase 1.

Rustemeier will send

—//—

Bayesian

A proposal should

① Show how & why bayesian might give an advantage - what is the quality of such an advantage - with classical clinical examples which should then go on to say how similar advantages would apply to ETS epidemiology for lung cancer.
Bayesian should give more defined definition of possible role of confounders - so that it would be more easily understandable the role of confounders ie actual strength of primary causes, their combinations, & possible confounders

② Suggestion public concern inversely related to evidence! -
evidence for cancer ≤ maternal sm < resp disorders.
public concern cancer > Mat. sm > resp disorders
"Working Group on Passive Smoking" - Paper (Reynolds)
This may effect the acceptance of reevaluation of data.
∴ non-neoplastic respiratory disorders may be a suitable subject for investigation.
But it may be that in order to fully exploit the Bayesian advantages

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Source: https://www.industrydocuments.ucsf.edu/docs/qscl0000

further data may be needed. - Recomendations for further reseach as from working group may be suitable. - clinical correlates of pulm fun. improved charact of suscept groups & high risk groups.

Model: should contain ① statement of goal of respect causality assessment.
② Structure of parametric model * (heirarchy of steps in deriving model)
③ identify prior conditions which v considered as background.
④ All adverse event types which will be analysed should be listed.
⑤ Exhaustive list of different possible causes & how to establish such into a mutually exclusive list - should be explained.
⑥ Estimation of prior odds & prior distributions.
⑦ Likelyhood functions should be specified

Data - proposal should include extent & type of data on LC.
If necessary simulated data should be used to validate parts of the model otherwise not testable.

Evaluation
Rules of planned evaluation should be given.
Terminology of results.
How results can be compared to classical & what criteria will be necessary to lead to the conclusion of that Bayesian Approach was superior.

—#—

Oey -

Spitzer et al - Links between Passive Smoking & Disease A Best synthesis.

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Source: https://www.industrydocuments.ucsf.edu/docs/qscl0000

10/11/92

ETS and allergies in children

656
P30 649
11:30 655

Claims: Especially in sweden - ETS said to be the main reason behind the increasing allergy figures among children.
Some news items say allergic increases more due to 4 bigs in indoor air quality in general.

Respond to this with scientific information on the rate of allergies and their possible causes -
Questions that need answering:

① Is there a real increase in allergic disorders in children? What is the evidence for this?
② In the literature what has been indicated including ETS as an inducer of such allergies?
③ What is the evidence behind the information on allergies caused by ETS or other factors?

Why would exposure to ETS increase allergy - surely childhood exposure to ETS is not increasing at present.

① Dont have any absolute figures on increases in ~~Atopy~~ allergic diseases for children on hand, but if there has been a recent increase in such disorders this would surely argue against ETS as a cause as there is no reason to believe that children are exposed to more ETS in recent years than previously - (If anything I would have thought that declining smoking statistics in many western countries would suggest decreasing exposure to ETS for children) I believe that if we looked further into the statistics we may find that increases in air pollution (indoor & outdoor) are more likely to parallel said increases in allergic responses. In order to follow this up more I would need more details on the basis of the statistics used to indicate the aforementioned increasing allergy figures in smoking children
② From a more scientific point of view I have ~~to~~ made a very preliminary review of some of the articles that we have on

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Source: https://www.industrydocuments.ucsf.edu/docs/qsci0000

allergic diseases.

Findings:

① Children whose parents smoke are more likely to be referred for allergic evaluation, but passive exposure to cigarette smoke does not lead to increased allergen specific IgE. This might suggest that in a general population based there are more ETS exposed children identified for allergic diseases than non-ETS exposed - but this would be due to a bias in the larger number being analysed in the former group and would not imply an increased underlying level in the ETS exposed population compared to non-ETS exposed.

② Pet ownership not associated w allergy? - No!

③ The epidemiological data with respect to long term effects of ETS exposure on adult asthmatics are inconclusive etc etc.

④ Environmental risk factors that may place inner-city children at ↑ risk for asthma include smoking, air pollution, overcrowding poorly vented heating & cooking gases, presence of house-dust mites & roaches & presence of pets.

Frischer et al. (1992). J. Pediatr. 1992; 126: 17-22.

Maternal smoking in early childhood: A risk factor for bronchial responsiveness to exercise in primary-school children.

Cigarette smoke exposure at age 1 year was associated with a higher proportion of children with BHR than with children with smoke exposure during the study year (6.6%). A change in maternal smoking habits seemed to influence the prevalence of BHR. Cigarette smoke exposure that occurred exclusively during the first year was associated with the highest prevalence of BHR (13.7%). Of children who continued to be exposed to cigarette smoke 7.6% were hyperresponsive, of children never exposed to smoke, 6.3% were hyperresponsive. The lowest proportion of children with BHR was observed in those exposed exclusively during the

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Source: https://www.industrydocuments.ucsf.edu/tobacco

study year (4.490).

Asthma & Allergies. Nordic Meeting :- identify consultant - Ring Stig Nilssen.

Nordic Allergy Conference - Stockholm.

Brochures for Phil

Ring Ingemo Bannier - Monday.

References :-

Barbara Shulte-Hobein et al Acta Paediat 81: 650-7 1992.

"Cigarette smoke exposure and development of infants throughout the first year of life: influence of passive smoking and nursing on cotinine levels in breast milk and infants urine"

"A retardation in mental development of children whose mothers smoked throughout pregnancy, which had previously been described by others, was not confirmed by our results. It appears that differences in mental development, influenced by manifold genetic and environmental sources, cannot easily be explained by a single cause such as smoke exposure."

Anders Hakansson & Bertil Carlsson Scand. J. Prim. Health Care 1992: 10: 60-65.

"Maternal Cigarette Smoking, Breast feeding, and Respiratory Tract Infections in Infancy".

Claim that maternal smoking has an effect on childhood R.T.I independant of that of the length of breast feeding. In fact in this study duration of breast feeding did not have any significant influence on R.T.I.

G.C. Windham et al, 1992 Amer. J. Epidem. 135(12): 1394-1403.

"Parental Cigarette Smoking and the risk of Spontaneous Abortion"

Good reviews of other literature pertaining to this subject in

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Source: https://www.industrydocuments.ucsf.edu/docs/qscl0000

the introduction and discussion' –

"In Conclusion, an association of active smoking with spontaneous abortion is not apparent in these data or in numerous other studies, although a moderate association with passive smoking was seen in this study."

+

Donald R Mattison, Environmental Research 28: 410-433 (1982)

The Effects of Smoking on fertility from Gametogenesis to implantation.

Comprehensive review but old!

+

Breast Cancer and Cigarette Smoking. A Hypothesis.
Palmer et al, 1991. Amer. J. Epidem. 134(1): 1-13.

Evaluation of two independent case control studies show positive relationship between cigarette smoking and Breast Cancer
= Weak associations between heavy smoking and risk of Breast Cancer
Association with age at commencement.

Letters in response to this report call for further analysis and inclusion of passive smoking data.

Letter from Denmark - Ewertz et al - does not support the relationship - in fact if anything shows a negative relationship.

+

J. Pawlega 1992. Acta Oncologica; 31(4): 384.

Breast Cancer and Smoking, Vodka Drinking and Dietary Habits.

No link with smoking. Vodka = OR 4.4.

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Source: https://www.industrydocuments.ucsf.edu/docs/qscl0000

T.A. Sellers et al. Cancer 1992;69;86-91.

"Lung Cancer Histologic Type and Family History of Cancer."

No evidence of a strong familial gene for site specific or histologic specific lung cancer. Genetic control may be through some sort of susceptibility to environmental agents.

T. A. Sellers et al. Cancer Research 52; 2691s - 2697s. 1992.

Smoking differences and lung Cancer Susceptibility

Presents further information on susceptibility - not genetic predisposition to lung cancer per se but rather a predisposition to the acts of the agents. In fact state that virtually all lung cancer occurs among gene carriers but without environmental incidence e.g. smoking the gene is not effective - i.e. it is not (lung cancer) a principally genetic disease.

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Source: https://www.industrydocuments.ucsf.edu/docs/qscl0000

MONTHLY ACTIVITIES - NOV. RDE.

① 2-3rd Attended U.S. - ITALY Workshop on Molecular Epidemiology in Genova

② 11th Visited John Wahren, Stockholm - to discuss consultancy & Nicotine vac.

③ 12th Visited Prof. O. Nilsen, Trondheim

④ 14th In Oslo - Research update for T. Mueller. Project Nicotine in Hair.

⑤

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Source: https://www.industrydocuments.ucsf.edu/docs/

OCTOBER 1992

1. NY - CSA meeting 6-7th
2. 8/10/92 - Angelo Cerdi - London
3. B&M training 16/10
4. 30/10 Nicomia Patel

Reviews:-

Trichopoulos

2028541405

Source: https://www.industrydocuments.ucsf.edu/docs/qscl0000

2028541406

Source: https://www.industrydocuments.ucsf.edu/docs/qscl0000